Journal of the American College of Cardiology Vol. 57, No. 21, 2011

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.01.034

Cardiac Imaging

Association of Annular Calcification and Aortic Valve Sclerosis With Brain Findings on Magnetic Resonance Imaging in Community Dwelling Older Adults

The Cardiovascular Health Study

Carlos J. Rodriguez, MD, MPH,* Traci M. Bartz, MS,† W. T. Longstreth, Jr, MD, MPH,‡ Jorge R. Kizer, MD, MSc,§ Eddy Barasch, MD,‖¶ Donald M. Lloyd-Jones, MD, MSc,# John S. Gottdiener, MD**

Winston-Salem, North Carolina; Seattle, Washington; New York, Roslyn, and Stony Brook, New York; Chicago, Illinois; and Baltimore, Maryland

Objectives The objective of this study was to investigate the associations of mitral annular calcification, aortic annular calcification, and aortic valve sclerosis with covert magnetic resonance imaging (MRI)–defined brain infarcts.

Background Clinically silent brain infarcts defined by MRI are associated with increased risk for cognitive decline, dementia, and future overt stroke. Left-sided cardiac valvular and annular calcifications are suspected as risk factors for clinical ischemic stroke.

Methods A total of 2,680 CHS (Cardiovascular Health Study) participants without clinical histories of stroke or transient ischemic attack underwent brain MRI in 1992 and 1993, 1 to 2 years before echocardiographic exams (1994 to 1995).

Results The mean age of the participants was 74.5 ± 4.8 years, and 39.3% were men. The presence of any annular or valvular calcification (mitral annular calcification, aortic annular calcification, or aortic valve sclerosis), mitral annular calcification alone, or aortic annular calcification alone was significantly associated with a higher prevalence of covert brain infarcts in unadjusted analyses ($p < 0.01$ for all). In models adjusted for age, sex, race, body mass index, physical activity, creatinine, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking, diabetes, coronary heart disease, and congestive heart failure, the presence of any annular or valve calcification remained associated with covert brain infarcts (risk ratio: 1.24; 95% confidence interval: 1.05 to 1.47). The degree of annular or valvular calcification severity showed a direct relation with the presence of covert MRI findings.

Conclusions Left-sided cardiac annular and valvular calcifications are associated with covert MRI-defined brain infarcts. Further study is warranted to identify mechanisms and determine whether intervening in the progression of annular and valvular calcification could reduce the incidence of covert brain infarcts as well as the associated risk for cognitive impairment and future stroke. (J Am Coll Cardiol 2011;57:2172–80) © 2011 by the American College of Cardiology Foundation

Mitral annular calcification (MAC), aortic annular calcification (AAC), and aortic valve (AV) sclerosis (AVSc) are characterized by calcium and lipid deposition on the fibrous skeleton at the base of the heart (mitral and aortic annuli)

From the *Department of Epidemiology and Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina; †Department of Biostatistics, University of Washington, Seattle, Washington; ‡Departments of Neurology and Epidemiology, University of Washington, Seattle, Washington; §Departments of Medicine and Public Health, Weill Cornell Medical College, New York, New York; ‖St. Francis Hospital, Roslyn, New York; ¶Stony Brook University, Stony Brook, New York; #Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois; and the **Department of Medicine, University of Maryland, Baltimore, Maryland. This research was supported by contract numbers N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, and N01-HC-45133 and grant number U01 HL080295 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. A full list of principal Cardiovascular Health Study investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm. Dr. Rodriguez is partially supported by the Robert Wood Johnson Foundation Amos Medical Faculty Development Program and a National Heart, Lung, and Blood Institute Mentored Patient-Oriented Research Career Development Award (K23 HL079343-01A3).

Manuscript received July 24, 2010; revised manuscript received December 10, 2010, accepted January 2, 2011.

and on the aortic cusps, respectively (1–4). Clinical precursors of atherosclerosis are also risk factors for MAC and AVSc (5). MAC and AVSc have been documented to be independent predictors of cardiovascular events (5,6), although their relationship with clinical ischemic stroke remains less well defined. Not all studies examining the association between MAC and stroke have reported a significant relationship (7–12), whereas an association between AV calcification and overt stroke has been demonstrated only in the presence of AV stenosis and not with AVSc (13).

With the increased use of magnetic resonance imaging (MRI), covert brain infarcts and white matter lesions (WMLs) are often seen in elderly people free of prior clinical transient ischemic attacks (TIA) and stroke (14–16). These covert MRI findings are not benign, because they are associated with cognitive decline and future overt stroke (17). Covert brain infarcts and WMLs are thought to have a vascular origin possibly related to microembolism along with microvascular ischemia (18). Data are lacking on the prevalence and relevance of these covert MRI findings in patients with MAC, AAC, and AVSc and without histories of TIA and stroke. Whether cardiac annular and valvular calcification is related to prevalent covert brain infarcts and WMLs independent of known and putative stroke risk factors remains untested.

The CHS (Cardiovascular Health Study) is a large, community-based study of cardiovascular disease in the elderly that included cranial MRI and echocardiography. We used data from the CHS to investigate the hypothesis that the prevalence of covert brain infarcts and WMLs would be higher in participants with MAC and calcific AV disease (defined as AVSc and AAC) than those without.

Methods

Study population. Details of the CHS have been published elsewhere (19,20). Briefly, a random sample of men and women age 65 years and older were recruited from Medicare eligibility lists in 4 U.S. communities (Sacramento County, California; Washington County, Maryland; Forsyth County, North Carolina; and Pittsburgh, Pennsylvania). In 1989 and 1990, the original study enrolled 5,201 subjects, and in 1992 and 1993, an additional 687 African Americans were enrolled. Exclusions included the use of a wheelchair, institutionalization, inability to give informed consent, plans to move away from the area within 3 years, or active treatment for malignancy. Each participating center received institutional review board approval, and all participants gave informed consent.

Of the 5,888 elderly participants in the CHS, 3,101 underwent both MRI in 1992 or 1993 and echocardiography in 1994 or 1995. We excluded 245 participants with clinical histories of stroke or TIA before their MRI or echocardiography. An additional 140 subjects were excluded in whom necessary variables from the MRI or echocardiographic studies could not be defined, as were 36 participants who were missing covariate information. Thus, the sample size for our primary analysis of covert brain infarcts was 2,680 participants. When WMLs were analyzed, our sample included 2,665 participants, because 15 participants were further excluded for lack of a WM grade measurement.

Abbreviations and Acronyms

- **AAC** = aortic annular calcification
- **AV** = aortic valve
- **AVSc** = aortic valve sclerosis
- **CHD** = coronary heart disease
- **CRP** = C-reactive protein
- **HDL** = high-density lipoprotein
- **LV** = left ventricular
- **MAC** = mitral annular calcification
- **MRI** = magnetic resonance imaging
- **NT-proBNP** = N-terminal pro-brain natriuretic peptide
- **TIA** = transient ischemic attack
- **WM** = white matter
- **WML** = white matter lesion

Measurements. The baseline examination (closest to and before MRI) included a standardized interview conducted by trained CHS study personnel assessing demographics, plus a variety of risk factors, including smoking, alcohol intake, history of TIA, stroke, congestive heart failure, and prior coronary heart disease (CHD). The physical examination included standardized measurements of height, weight, and seated blood pressure measured using a random-zero sphygmomanometer. Blood pressure was measured in triplicate 5 minutes apart. All patients were instructed to fast. Diabetes was defined as a clinical history of diabetes, fasting glucose level >126 mg/dl, or the use of a diabetic medication. Lipid measurements were made at the Laboratory for Clinical Biochemistry Research, and low-density lipoprotein was calculated using the Friedewald equation.

Echocardiography. Two-dimensional echocardiograms were recorded on videotape using a Toshiba SSH-160A ultrasound machine (Toshiba Corporation, Tokyo, Japan) during the 1994 and 1995 CHS examinations, as detailed previously (21,22). The echocardiograms were evaluated at a centralized core laboratory (Georgetown University, Washington, DC) by observers blinded to participants' clinical histories.

Definitions of AVSc, MAC, and AAC were the same as in previous CHS studies (2,23). AVSc was identified as focal or diffuse aortic cusp thickening, stiffness, and/or increased echogenicity (calcification) with normal aortic cusp excursion and a peak trans-AV flow velocity <2.0 m/s. MAC was defined by increased echodensity located at the junction of the atrioventricular groove and posterior mitral leaflet on the parasternal long-axis, short-axis, or apical 4-chamber view. The presence of AAC was similarly defined as increased echodensity of the aortic root at the insertion of the aortic cusps.

MRI. Brain MRI was performed during the 1992 and 1993 CHS examinations, 1 to 2 years before the echocardiographic exams. Brain MRI was performed and interpreted without any information about the participant, as

previously described (24). A brain infarct was defined as an area of low signal intensity of at least 3 mm on T1-weighted images that was also visible as a hyperintense lesion on T2-weighted images. MRI-defined brain infarcts were categorized as absent or present. WMLs were considered present if visible as hyperintense on proton-density and T2-weighted images, without prominent hypointensity on T1-weighted scans. WMLs were assigned a grade from 0 (best) to 9 (worst) and analyzed as a dichotomous variable with WM grade >4. Covert MRI findings were defined as: 1) high WM grade of 5 or more; 2) the presence of infarcts; or 3) both. Infarct location was determined as cortical infarcts (any infarct involving the cortex or the cerebellar surface) and noncortical infarcts (any infarct involving basal ganglia, thalamus, internal capsule, or centrum ovale and sparing the cortical surface). Noncortical infarcts were almost entirely <20 mm (25).

Secondary exposure variables. Echocardiographic left atrial dimensions (in centimeters) were defined in the parasternal long-axis view, as described (26). Measurement of left ventricular (LV) internal dimensions in diastole was used to determine LV mass using an established validated method (26). LV mass was normalized for height$^{2.7}$ according to published guidelines (26). LV hypertrophy was defined on the basis of established LV mass cutoffs (26). Atrial fibrillation was determined on electrocardiography at the time of examination or by self-report at any visit up through the last visit before the MRI. Measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP) was performed using a commercially available immunoassay (Elescys proBNP Assay, Roche Diagnostics, Indianapolis, Indiana) on the Elescys 2010 instrument. High-sensitivity C-reactive protein (CRP) measurement was performed using a latex-enhanced reagent (Dade Behring, Deerfield, Illinois). Cystatin C concentration was measured using a BNII nephelometer (N Latex Cystatin-C, Dade Behring). NT-proBNP, CRP, and cystatin C were all log transformed and analyzed as continuous variables.

Statistical analysis. We performed a cross-sectional analysis in participants without histories of clinical TIA or stroke. Echocardiographic variables of annular and valvular calcification were our exposure variables to be related to the presence of MRI findings. Because the prevalence of brain infarcts was close to 27% in our population, unadjusted and adjusted risk ratios and 95% confidence intervals were calculated by relative risk regression (27) using Poisson regression with robust standard errors. MAC, AAC, and AVSc were analyzed as separate and combined independent variables. Analyses tested whether: 1) MAC was related to brain infarct; 2) MAC was related to high WM grade; and 3) MAC was related to any MRI finding. This analysis was repeated for AAC and AVSc, as well as for combined measures of annular and valvular calcification. Specifically, the variable "any annular or valvular calcification" included the presence of MAC, AAC, or AVSc, whereas the variable "all annular or valvular calcification" included the presence of MAC, AAC, and AVSc together; "any AV calcification" included AAC and AVSc. Our primary exposure of interest, specified a priori, was the presence of the combined measures of any annular or valvular calcification. The primary outcome of interest was the presence of covert brain infarcts. All other exposure and outcome measures were secondary. Potential confounders associated with annular or valvular calcification and established stroke risk factors were included in adjusted models: model 1 (age, sex, and race adjusted) and model 2 (adjusted for age, sex, race, body mass index, physical activity, creatinine, average systolic blood pressure, total cholesterol, high-density lipoprotein [HDL] cholesterol, smoking, diabetes, and the presence of CHD or congestive heart failure at the closest clinic visit before MRI). On the basis of their known associations with cerebrovascular events (left atrial enlargement, atrial fibrillation, and LV hypertrophy) or their potential role as mediators or confounders (NT-proBNP, CRP, and cystatin C), independent predictor variables were analyzed in a priori exploratory models: model 3 (model 1 plus LV hypertrophy and left atrial enlargement) and model 4 (model 1 plus atrial fibrillation, CRP, NT-proBNP, and cystatin C). We used chi-square and regression analysis to examine associations in strata defined by infarct location: cortical infarct versus noncortical infarct. Subjects with multiple infarcts were included in the cortical infarct group if at least 1 infarct was cortical and in the noncortical group if all infarcts were noncortical. In regression analyses, those infarcts not of the type being examined in the particular stratum were excluded. Stata version 10.1 (StataCorp LP, College Station, Texas) was used for all analyses.

Results

The mean age of the participants in these analyses was 74.5 ± 4.8 years, and 39.3% were men. MAC was found in 40.1%, AAC in 44.3%, and AVSc in 53.3%. The prevalence of any annular or valvular calcification was 77.0%, whereas the prevalence for all calcification was 16.0%. Age, creatinine level, male sex, white race, history of CHD, NT-proBNP, and cystatin C levels were all associated with annular or valvular calcification (MAC, AAC, or AVSc) in bivariate comparisons (Table 1). Neither total cholesterol nor HDL cholesterol individually showed a significant association with any annular or valvular calcification ($p = 0.08$), but the ratio of total cholesterol to HDL cholesterol did ($p = 0.03$).

Effects on covert brain infarcts. On MRI, 712 participants (26.6%) had 1 or more covert infarcts, and 161 (6.0%) had WM grades >4. The presence of covert brain infarcts was significantly associated with detection of any annular or valvular calcification ($p = 0.001$) in bivariate comparisons (Fig. 1). Relative risk regression analysis showed that any annular or valvular calcification, MAC, AAC, and any AV calcification were associated with the presence of covert brain infarcts in unadjusted models (Table 2). In minimally

Table 1 Descriptive Statistics for the Total Study Cohort and According to Annular or Valvular Calcification Status

Risk Factor	Entire Cohort (n = 2,680)	Any Annular or Valve Calcification* (n = 2,063)	No Annular or Valve Calcification (n = 617)	p Value
Age (yrs)	74.53 ± 4.81	74.79 ± 4.87	73.67 ± 4.52	<0.0001
BMI (kg/m^2)	26.68 ± 4.37	26.62 ± 4.31	26.86 ± 4.56	0.22
Men	1,053 (39.3%)	842 (40.8%)	211 (34.2%)	0.003
White race	2,275 (84.9%)	1,769 (85.8%)	506 (82.0%)	0.02
Physical activity (kcal)	1,620.59 ± 1,837.96	1,621.16 ± 1,850.79	1,618.67 ± 1,795.90	0.98
Serum creatinine (mg/dl)	1.03 ± 0.26	1.04 ± 0.27	1.01 ± 0.22	0.003
Systolic BP (mm Hg)	134.22 ± 20.13	134.20 ± 19.82	134.28 ± 21.15	0.93
TC/HDL cholesterol ratio	4.09 ± 1.22	4.12 ± 1.21	3.99 ± 1.24	0.027
TC (mg/dl)	209.31 ± 37.34	210.00 ± 37.55	207.00 ± 36.56	0.081
HDL cholesterol (mg/dl)	54.40 ± 14.73	54.12 ± 14.61	55.32 ± 15.07	0.076
Smoking status				
Never smoker	1,224 (45.7%)	923 (44.7%)	301 (48.8%)	
Former smoker	1,219 (45.5%)	963 (46.7%)	256 (41.5%)	
Current smoker	237 (8.8%)	177 (8.6%)	60 (9.7%)	0.07
Diabetes prevalence	317 (11.8%)	247 (12.0%)	70 (11.4%)	0.85
Presence of CHD	466 (17.4%)	380 (18.4%)	86 (13.9%)	0.01
Presence of CHF	92 (3.4%)	77 (3.7%)	15 (2.4%)	0.12
CRP (mg/dl)	4.68 ± 7.71	4.68 ± 8.02	4.68 ± 6.57	0.99
Natural log of NT-proBNP	229.08 ± 427.25	245.57 ± 466.02	171.80 ± 241.27	0.0006
Natural log of cystatin C	1.07 ± 0.26	1.08 ± 0.27	1.05 ± 0.21	0.003
Left atrial size (cm)	4.00 ± 0.93	4.01 ± 1.01	3.94 ± 0.58	0.084
Atrial fibrillation	202 (7.5%)	173 (8.4%)	29 (4.7%)	0.002
LV hypertrophy	474 (24.4%)	18 (26.3%)	91 (18.8%)	0.001

Data are mean ± SD and n (%). *Any annular or valve calcification combines the presence of mitral annular calcification, aortic annular calcification, or aortic valve sclerosis.
BMI = body mass index; BP = blood pressure; CHD = congenital heart disease; CHF = congestive heart failure; HDL = high-density lipoprotein; LV = left ventricular; NT-proBNP = N-terminal pro-brain natriuretic peptide; TC = total cholesterol.

adjusted models, the presence of MAC, any AV calcification, and any annular or valvular calcification were associated with covert brain infarcts. In models adjusted for age, sex, race, body mass index, physical activity, systolic blood pressure, smoking, diabetes, total cholesterol, HDL cholesterol, creatinine, CHD, and congestive heart failure, only the presence of any annular or valve calcification was associated with covert brain infarcts. Additional a priori exploratory models (models 3 and 4) adjusting for factors such as LV hypertrophy, left atrial size, NT-proBNP, CRP, atrial fibrillation, and cystatin C did not meaningfully change the results (Table 2). When all annular or valvular calcification was included as the exposure variable, only unadjusted and minimally adjusted models were statistically significant (data not shown).

Effects on high WM grade. With high WM grade as the outcome, the presence of any annular or valvular calcification, the presence of any AV calcification, and the presence of AAC were significant determinants associated in unadjusted models. Only the presence of any annular or valvular calcification was associated with high WM grade in minimally adjusted and fully adjusted models. The association of any AV calcification with WM grade was only marginally significant (Table 3).

Effects on covert brain infarcts and high WM grade. When high WM grade and brain infarcts were considered as a combined outcome (Table 4), the results were consistent with our above models. The presence of any annular or valvular calcification, any AV calcification, MAC, and AAC showed significant associations with combined outcomes in our unadjusted and minimally adjusted models. In our fully adjusted model and exploratory models, only the presence of any annular or valvular calcification, the presence of any AV calcification, and the presence of AAC were related to the combined outcome. AVSc alone was not associated with any brain MRI finding in any of our models. The degree of valvular calcification showed a direct relation with the presence of covert brain MRI lesions. In fully adjusted models, moderate to severe annular or valvular calcification in the mitral and aortic position showed a 21% and 19% higher risk for covert brain infarcts and a 51% and 38% higher risk for covert brain infarcts and/or high WM grade than no valvular lesions, respectively, although the difference was statistically significant only for the relation of AV lesions with covert brain infarcts (Figs. 2 and 3).

Infarct location analysis. Of the 712 participants with covert infarcts, 65 (9%) had any cortical infarcts and 647 (91%) had noncortical infarcts. The prevalence of cortical infarcts versus noncortical infarcts in those with versus without any annular or valvular calcification was not significantly different (p = 0.51). Relative risk regression analysis of any annular or valvular calcification using

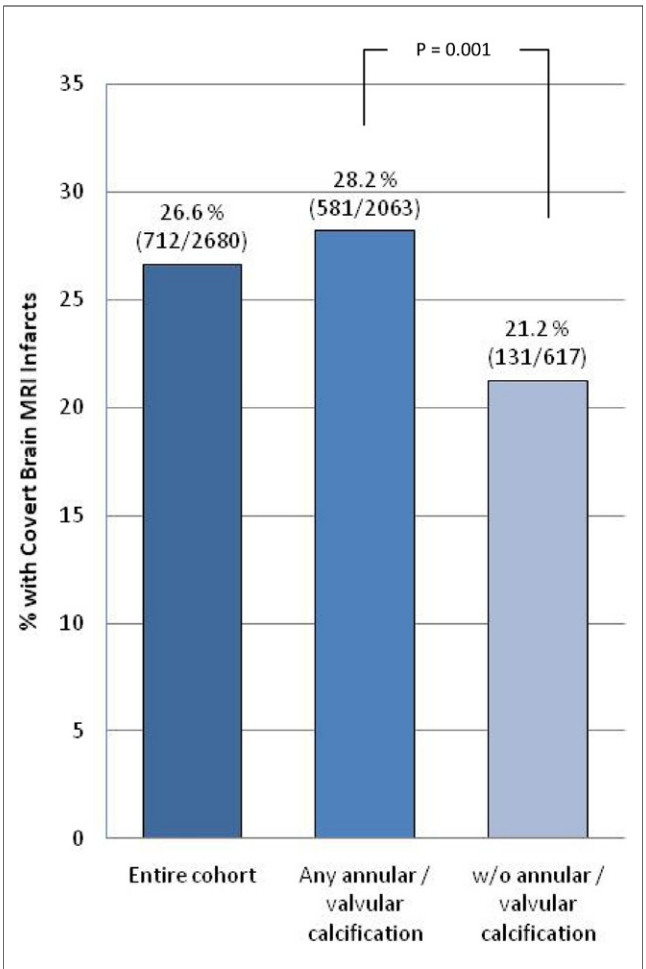

Figure 1 Proportion of Participants With Covert Brain Infarcts According to Annular or Valve Lesion Status

Data showing a significantly greater proportion of covert brain infarcts in participants with any annular or valvular calcification compared with those without any annular or valvular calcification. MRI = magnetic resonance imaging.

model 2 showed that risk ratios were only slightly stronger for any cortical infarct than for noncortical infarcts, but as expected given the small number of cortical infarcts, the association for this stratum was not significant (Table 5).

Discussion

In a community-based sample of older adults, we found that the presence of any left-sided cardiac annular or valvular calcification was significantly associated with a 33% greater risk for covert brain infarcts on MRI in participants without histories of TIA or stroke. This observed association persisted after full adjustment for potential confounders. Similar associations were observed with the presence of high WM grade and when covert brain infarcts and high WM grade were analyzed as a combined MRI-defined outcome. Additionally, we used explanatory models with comprehensive adjustment for clinical confounders and echocardiographic and inflammatory covariates. Our findings remained independent of NT-proBNP, CRP, and cystatin C, suggesting that the primary association represents more than simply shared risk factors.

Prior studies have reported inconsistent findings with respect to the association between left-sided cardiac annular or valvular calcifications and the risk for clinical stroke. MAC and AAC are characterized by calcium and lipid deposition in the annular fibrosa, whereas AVSc results from similar accumulation involving the AV leaflets (1,28). Although numerous case reports provide evidence of brain infarction due to calcific emboli from AVs (29–33), an independent association between AV calcification and clinical stroke has been demonstrated only in the presence of hemodynamically significant AV stenosis (4,13). Several studies (7,9,10) have detailed a relationship between MAC and clinical stroke, but this was not confirmed by a prior report from the CHS or by a separate study using a matched control group (3,8,34). The weight of the evidence, although varied and seemingly conflicted, favors the presence of some association between mitral and/or aortic calcification and clinical ischemic stroke.

To our knowledge, our study is the first to demonstrate an association between left-sided cardiac annular or valvular calcifications and covert brain infarcts. Most studies of calcific AV disease do not detail the presence of concomitant AAC, and it may be that AAC is an underappreciated exposure in stroke risk. Our results are important because

Table 2 Risk Ratios (95% Confidence Intervals) Describing the Associations Among MAC, AAC, and AVSc and Covert Brain Infarcts

Variable	Unadjusted	p Value	Model 1	p Value	Model 2	p Value	Model 3	p Value	Model 4	p Value
Any annular or valve calcification	1.33 (1.12–1.57)	0.001	1.27 (1.08–1.50)	0.005	1.24 (1.05–1.47)	0.011	1.24 (1.02–1.50)	0.035	1.27 (1.05–1.53)	0.013
MAC	1.21 (1.06–1.37)	0.003	1.15 (1.01–1.30)	0.035	1.12 (0.99–1.27)	0.081	1.09 (0.93–1.27)	0.303	1.11 (0.97–1.28)	0.140
AAC	1.17 (1.03–1.33)	0.014	1.11 (0.98–1.26)	0.108	1.09 (0.96–1.24)	0.179	1.09 (0.93–1.27)	0.290	1.08 (0.94–1.24)	0.288
AVSc	1.08 (0.95–1.23)	0.224	1.07 (0.94–1.21)	0.323	1.04 (0.92–1.18)	0.538	1.05 (0.90–1.22)	0.559	1.08 (0.93–1.24)	0.313
Any AV calcification*	1.21 (1.05–1.41)	0.009	1.16 (1.00–1.35)	0.044	1.14 (0.99–1.32)	0.075	1.11 (0.93–1.32)	0.240	1.15 (0.98–1.35)	0.096

*Any AV calcification: combination of AAC or AVSc. Model 1: adjusted for age, sex, and race (white, nonwhite). Model 2: adjusted for age, sex, race, body mass index, physical activity, creatinine, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking status (never, former, current), diabetes, and the presence of coronary heart disease or congestive heart failure at closest clinic visit before brain magnetic resonance imaging. Model 3: adjusted for age, race, sex, left ventricular hypertrophy, and left atrial dimension. Model 4: adjusted for age, race, sex, N-terminal pro-brain natriuretic peptide, C-reactive protein, cystatin C, and atrial fibrillation.

AAC = aortic annular calcification; AV = aortic valve; AVSc = aortic valve sclerosis; MAC = mitral annular calcification.

Table 3 Risk Ratios (95% Confidence Intervals) Describing the Associations Among AVSc, MAC, and AAC and High WM Grade (>4)

Variable	Unadjusted	p Value	Model 1	p Value	Model 2	p Value	Model 3	p Value	Model 4	p Value
Any annular or valve calcification	1.8 (1.17–2.77)	0.008	1.59 (1.04–2.45)	0.033	1.61 (1.04–2.49)	0.033	1.65 (0.98–2.77)	0.058	1.63 (0.99–2.70)	0.055
MAC	1.34 (0.99–1.81)	0.055	1.14 (0.85–1.54)	0.390	1.16 (0.86–1.57)	0.334	1.13 (0.79–1.62)	0.510	1.12 (0.80–1.58)	0.502
AAc	1.48 (1.10–2.00)	0.010	1.25 (0.92–1.69)	0.154	1.23 (0.91–1.68)	0.177	1.29 (0.90–1.85)	0.173	1.23 (0.87–1.74)	0.237
AvSc	1.29 (0.95–1.76)	0.099	1.25 (0.92–1.69)	0.153	1.24 (0.91–1.68)	0.166	1.37 (0.94–1.99)	0.097	1.39 (0.98–1.97)	0.061
Any AV calcification*	1.64 (1.13–2.38)	0.009	1.44 (1.00–2.10)	0.053	1.45 (1.00–2.11)	0.050	1.60 (1.01–2.53)	0.045	1.49 (0.97–2.28)	0.068

*Any AV calcification: combination of AAC or AVSc. Model 1: adjusted for age, sex, race (white, nonwhite). Model 2: adjusted for age, sex, race, body mass index, physical activity, creatinine, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking status (never, former, current), diabetes, and the presence of coronary heart disease or congestive heart failure at closest clinic visit before brain magnetic resonance imaging. Model 3: adjusted for age, race, sex, left ventricular hypertrophy, and left atrial dimension. Model 4: adjusted for age, race, sex, N-terminal pro-brain natriuretic peptide, C-reactive protein, cystatin C, and atrial fibrillation.

Abbreviations as in Table 2.

covert MRI-defined brain infarcts and WMLs are associated with a higher risk for cognitive decline and future stroke (14,16,17). The implication of our findings is that the relationship between left-sided cardiac annular or valvular calcifications and brain infarcts may have been underestimated in prior studies that considered only clinical ischemic stroke. This relationship may be stronger and of greater clinical relevance when both covert and overt brain infarcts are considered.

Several explanations may account for the independent association of annular or valvular calcific lesions with covert MRI-defined brain infarcts. These cardiac lesions may not be just markers of stroke risk based on their association with atherosclerotic vascular disease (35,36) but may also play a causative role. Embolization from left-sided cardiac annular or valvular calcifications can vary from friable ulcerated calcium deposits to noncalcific (thrombus) embolization (32,37–40). Evidence of systemic embolism to cerebral, coronary, renal, and retinal arteries and the peripheral circulation has been found on autopsy in one-third of patients with calcific AV disease (30), with evidence of organized microthrombi observed in 53% of calcified AVs (41). Wilson et al. (32) noted calcific AV disease as the most common cardiac abnormality in patients with central retinal artery occlusion. A potential mechanistic pathway for microthrombi formation on left-sided calcified structures could involve turbulent blood flow at the mitral or aortic position, followed by fragmentation of red cells and release of adenosine diphosphate and thromboplastin, with resulting microthrombus formation and noncalcific embolism (41,42). The incidence of cerebral thromboembolism from left-sided cardiac annular or valvular calcifications is likely underestimated. Patients may remain asymptomatic in some cases depending on the size of emboli (30), and any neurologic symptoms may be attributed to other competing causes, such as low cardiac output, small vessel disease, or atrial fibrillation. A caveat to this argument is that most infarcts in the CHS were noncortical, which are typically not cardioembolic (25), suggesting that embolism may not be the only explanation for covert infarcts in those with annular or valvular calcification. The number of cortical infarcts in these CHS participants was not sufficient to answer the question of whether or not the risk for covert infarcts with any annular or valvular calcification differs by infarct location. In addition, the association between annular or valvular calcification may be through either known or unknown shared risk factors that were not considered in these analyses, such as atherosclerotic disease of the aorta and cervicocranial vasculature.

Regarding WM disease and annular or valvular calcification, the mechanism of association is somewhat unclear. WM disease is found in those with vascular dementia and may be the consequence of microvasculopathy, edema, gliosis, as well as chronic ischemia and small infarcts such as those caused by embolic calcific disease (43). Although it is true that both WM disease and annular or valvular calcifi-

Table 4 Risk Ratios (95% Confidence Intervals) Describing the Associations Among AVSc, MAC, and AAC and Either Covert Brain Infarcts or High WM Grade (>4)

Variable	Unadjusted	p Value	Model 1	p Value	Model 2	p Value	Model 3	p Value	Model 4	p Value
Any annular or valve calcification	1.39 (1.19–1.64)	<0.001	1.33 (1.13–1.56)	0.001	1.31 (1.11–1.54)	0.001	1.30 (1.07–1.57)	0.007	1.33 (1.11–1.59)	0.002
MAC	1.20 (1.07–1.35)	0.002	1.13 (1.00–1.27)	0.042	1.11 (0.99–1.25)	0.074	1.08 (0.93–1.25)	0.307	1.10 (0.96–1.25)	0.169
AAC	1.22 (1.09–1.38)	0.001	1.15 (1.02–1.29)	0.021	1.14 (1.01–1.28)	0.035	1.15 (0.99–1.32)	0.062	1.13 (0.99–1.29)	0.072
AVSc	1.10 (0.97–1.24)	0.123	1.08 (0.96–1.22)	0.201	1.06 (0.94–1.19)	0.326	1.06 (0.92–1.23)	0.394	1.09 (0.95–1.24)	0.212
Any AV calcification*	1.28 (1.11–1.47)	0.001	1.22 (1.06–1.40)	0.006	1.20 (1.05–1.39)	0.009	1.19 (1.01–1.40)	0.043	1.21 (1.04–1.41)	0.016

*Any AV calcification: combination of AAC or AVSc. Model 1: adjusted for age, sex, race (white, nonwhite). Model 2: adjusted for age, sex, race, body mass index, physical activity, creatinine, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking status (never, former, current), diabetes, and the presence of coronary heart disease or congestive heart failure at closest clinic visit before brain magnetic resonance imaging. Model 3: adjusted for age, race, sex, left ventricular hypertrophy, and left atrial dimension. Model 4: adjusted for age, race, sex, N-terminal pro-brain natriuretic peptide, C-reactive protein, cystatin C, and atrial fibrillation.

Abbreviations as in Table 2.

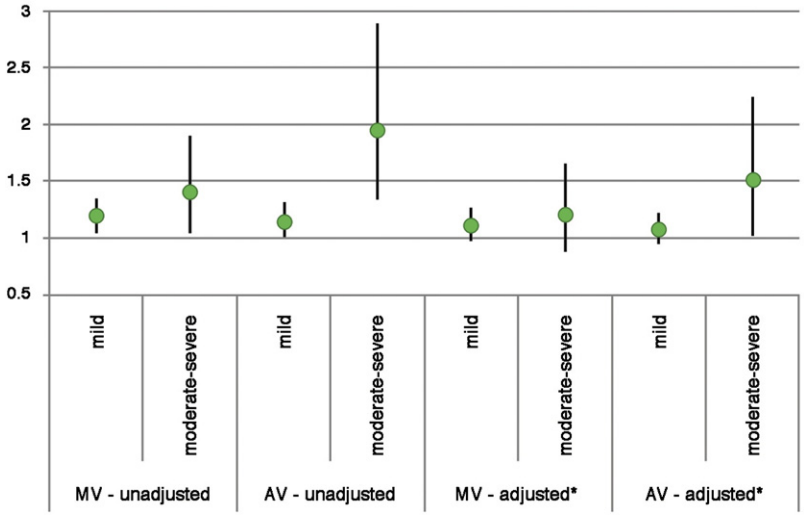

Figure 2 Risk Ratios by Valve Calcification Severity Predicting Covert Brain Infarcts

*Adjusted for age, sex, race, body mass index, physical activity, creatinine, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking, diabetes, and the presence of coronary heart disease or congestive heart failure at closest clinic visit before brain magnetic resonance imaging. Comparison group: those with no mitral valve (MV) or aortic valve (AV) calcification.

cation are common conditions in the elderly, such that their association may be coincidental, the independent association after adjusting for age and multiple confounders argues against a coincidence of common risk factors or residual confounding. Furthermore, the strength of association, as measured by risk ratios, for WM disease was greater than that for covert brain infarcts and annular or valvular calcification.

Strengths of our study include its large sample size and derivation from a well-defined community-based cohort. In the present study, 2-dimensional visualization of annular or valvular calcification may have allowed for the more accurate identification of calcification than was possible with M-mode examination performed in earlier published studies. In addition, we were able to adjust our models for

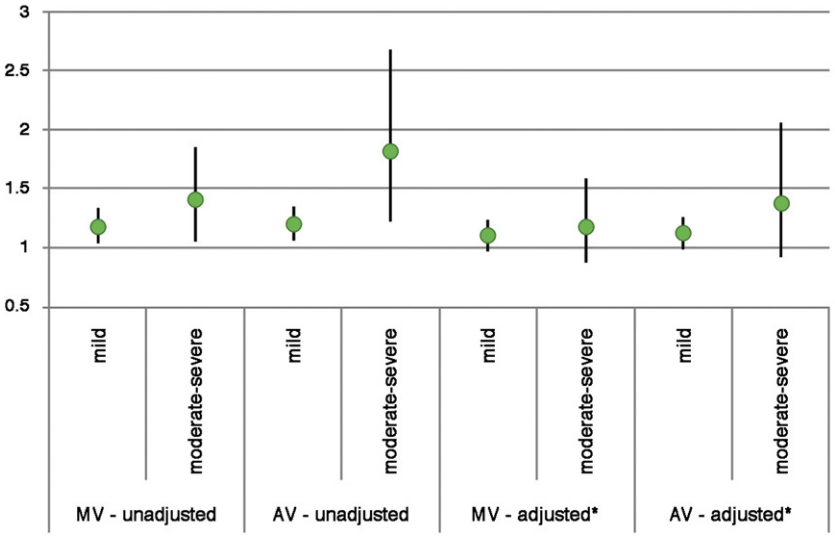

Figure 3 Risk Ratios by Valve Calcification Severity Predicting Either Covert Brain Infarcts and/or White Matter Lesions

*Adjusted for age, sex, race, body mass index, physical activity, creatinine, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking, diabetes, and the presence of coronary heart disease or congestive heart failure at closest clinic visit prior to brain magnetic resonance imaging. Comparison group: those with no MV or AV calcification. Abbreviations as in Figure 2.

Table 5 Covert Brain Infarct Location According to Calcific Annular or Valve Disease Status

Infarct Location	In Those Without Any Annular or Valve Calcification	In Those With Any Annular or Valve Calcification	Risk Ratio (95% Confidence Interval)*
Noncortical	18% (121/647)	81% (526/647)	1.23 (1.03–1.47)
Cortical	15% (10/65)	85% (55/65)	1.64 (0.84–3.21)

*Adjusted for age, sex, race, body mass index, physical activity, creatinine, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking status (never, former, current), diabetes, and the presence of coronary heart disease or congestive heart failure at closest clinic visit before brain magnetic resonance imaging.

markers of inflammation, echocardiographic variables, and other important potential confounders.

Our study also had several limitations. First, we performed brain MRI 1 to 2 years before the echocardiographic examinations. Thus, causality cannot be inferred. In doing this as a cross-sectional analysis, we are assuming that changes in measures determined on MRI are slow, so that those variables remain close to what they would be had they been obtained at the time of the echocardiographic examination. Although the issue of reverse causality exists, it is not biologically plausible that covert brain infarcts would cause annular or valvular calcification. Moreover, because such covert infarcts would not lead to immediate disability, there would be less of a short-term clinical impact of these lesions than would be observed from clinically apparent overt stroke. Second, although our statistical models were extensive, unmeasured confounders could potentially explain the observed associations. Third, our classification scheme for left-sided annular or valvular calcification can be criticized. MAC, AAC, and AVSc are distinct disease processes but with significant overlap and correlation characterized by common initial pathology of lipid infiltration, components of chronic inflammation, and calcification (28). This disease process is manifested and progresses differently, possibly because of different flow hemodynamic parameters between the mitral and aortic annuli. We looked at these cardiac lesions as an aggregate because of the threat of calcific and thrombotic systemic embolism, which is typically unique to left-sided lesions unless there is a patent foramen ovale present. We defined AV calcification as calcification within the AV leaflets or valve annulus. Thus, AAC, AVSc, and aortic stenosis represent different points along the same histopathologic spectrum. Last, the majority of CHS participants were Caucasian, possibly reducing the generalizability of our findings to other ethnic groups of older adults.

Conclusions

Our results indicate that left-sided cardiac annular or valvular calcification is associated with covert MRI-defined brain infarcts. Prior estimates of the association between calcific annular or valve disease and stroke may be underestimated, because they accounted only for clinical overt stroke. Further study is warranted to identify the mechanisms relating these 2 sets of findings in the heart and brain and determine whether intervening in the progression of calcific annular or valvular disease can reduce the incidence of these covert MRI findings as well as the associated risk for cognitive decline and future stroke.

Reprint requests and correspondence: Dr. Carlos J. Rodriguez, Division of Public Health Sciences, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, North Carolina 27157. E-mail: crodrigu@wfubmc.edu.

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Key Words: aortic valve ■ calcification ■ covert brain infarcts ■ epidemiology.